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Aims and Scope

Phlebolymphology **is an international scientific journal entirely devoted to venous and lymphatic diseases.**

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

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Content

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Editorial

Dear Readers,

In this new issue of *Phlebolymphology*, you will find the articles as below:

Deep vein obstruction associated with the lower limbs is common. **N. LABROPOULOS and A. JAVVAJI *(USA)***, discuss overcoming the diagnostic challenges in deep venous obstruction while addressing the integration of morphological and hemodynamic testing in clinical practice.

Over the past 15 years, interventional therapies targeting early thrombus removal have evolved as a potentially better alternative for good-risk patients with iliofemoral deep venous thrombosis, aiming to decrease postthrombotic syndrome rates or severity and improve quality of life. **E. AVGERINOS *(Greece)* and H. JALAIE *(Germany)*** summarize current evidence, novel technologies, and the technical approach to the management of iliofemoral deep venous thrombosis.

K. DESAI *(USA)* provides an up-to-date review on the management of chronic deep venous obstructive disease, including the epidemiology, the clinical course, and the endovascular management of upper- and lower-extremity venous obstructive disease.

Venous stenting has rapidly advanced over the last 10 years as the emergence of dedicated venous stents and advancement in thrombectomy devices has renewed interest in this field. **S. BLACK *(UK)*** presents the advancements in venous stenting while pointing out some of the problems that have arisen, as well as assesses the potential future developments that may be needed.

Enjoy reading this issue!

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Overcoming the diagnostic challenges in deep venous obstruction: the imperative integration of morphological and hemodynamic testing in clinical practice

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ABSTRACT

Deep vein obstruction (DVO) in the lower limbs stems from a range of underlying causes, encompassing both thrombotic and nonthrombotic origins. In some cases, preexisting nonthrombotic obstructions may evolve into thrombotic ones, a phenomenon exemplified in rare conditions like iliac vein compression aplasia or hypoplasia. The complex nature of DVO leads to differences in its clinical presentation and hemodynamic impact. The diverse clinical manifestations of DVO, ranging from asymptomatic cases to venous ulcers, may present challenges in the evaluation of this condition. In this article, we address limitations of common diagnostic methods such as ultrasound, intravascular ultrasound, venography, computed tomography venography, and magnetic resonance venography for DVO. Furthermore, we emphasize the need for a combined morphological and hemodynamic testing approach, as relying solely on one method often provides an incomplete picture of the obstruction's nature and symptom severity. Morphological testing focuses on visualizing the physical structure of the veins to identify any obstructions using factors such as stenosis, occlusions, collaterals, etc. Hemodynamic testing, on the other hand, examines the functional aspects of blood flow within the affected veins, providing information on blood pressure, velocity, and flow characteristics. By combining the 2 assessments, we can use an integrated approach to enhance diagnostic accuracy and develop personalized and efficacious treatment plans.

Keywords

deep venous obstruction | diagnosis | hemodynamic testing | morphological testing | nonthrombotic | positional stenosis | postthrombotic

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Introduction

Deep vein obstruction (DVO) associated with the lower limbs is common. The DVO pathophysiology is most often due to a previous episode of thrombosis, nonthrombotic causes, or the combination of the two. Nonthrombotic DVO or extraluminal venous obstruction is often attributed to venous compression.[1] Additionally, congenital anomalies, characterized by structural irregularities present since birth, can also contribute to nonthrombotic DVO. The incidence of congenital abnormalities among patients with DVO is less than 10%, and nonthrombotic cases typically manifest during the second decade of life.[2] A hemodynamically significant vein obstruction reduces blood flow, leading in some cases to ambulatory venous hypertension, which, in turn, causes the development of signs and symptoms related to chronic venous disease (CVD).

Postthrombotic obstruction arises from past episodes of deep venous thrombosis (DVT)

Postthrombotic obstruction is easier to diagnose and is more often associated with signs and symptoms. Nonthrombotic obstruction has a less clear association and is frequently asymptomatic.[2] Typically, postthrombotic lesions are longer than nonthrombotic lesions and the wall is less compliant. This causes the outflow resistance in patients with postthrombotic lesions to be higher, so they are more likely to be symptomatic. Nonthrombotic lesions are usually less symptomatic and have tighter lesions if they are symptomatic.[3]

In some cases, DVO can result from preexisting nonthrombotic obstructions but subsequently some individuals develop DVT. The latter can be the cause to unravel the nonthrombotic obstruction as many patients prior to DVT have no symptoms. Those that could have been symptomatic prior to DVT get worse when they develop thrombosis. Only 2% to 3% of DVT cases are associated with iliac vein compression (IVC).[2] An example of this case is IVC aplasia or hypoplasia, which are congenital abnormalities or are induced by a catheter insertion at younger ages that can also trigger thrombus formation. These conditions are rare and typically affect 0.5% of the general population.[4] Such lesions may be asymptomatic and are incidentally found through imaging. They could also cause the development of recurring thrombosis of the lower extremities and pelvic veins. IVC aplasia or hypoplasia should be suspected in patients younger than 30 years who present with proximal DVT. The following images *(Figure 1A and 1B)* demonstrate how obstruction presents in patients with such abnormalities.

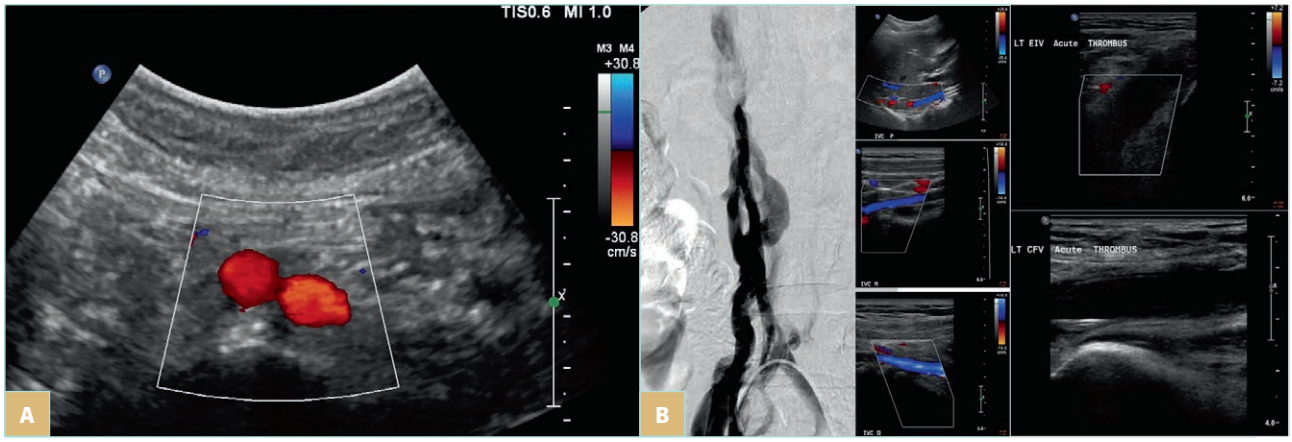

Figure 1. A) Iliac vein compression (IVC) aplasia in a young patient who presented with bilateral lower-limb edema. The infrarenal IVC and both common iliac veins were absent. The patient had no catheterization, and this is a case of congenital absence. In the image above, the aortic bifurcation is seen but the IVC is absent. The common iliac veins were absent too. There were many collateral veins in the subcutaneous space from the groin to the abdomen and many pelvic collaterals through both internal iliac veins. B) IVC hypoplasia in a young female who presented with deep venous thrombosis (DVT) from left calf to the common iliac veins. The venogram demonstrates the collateral veins around the hypoplastic IVC that has a diameter of 2-5 mm (first panel). The ultrasound images show the patent but hypoplastic IVC proximal, middle, and distal (center panel from top to bottom) and acute thrombosis in the left external iliac (top image on the third panel) and common femoral veins (bottom image).

Clinical presentation and hemodynamics of DVO

Patients with DVO have a wide range of clinical presentations, from being asymptomatic to venous claudication and ulceration. Many factors can affect clinical presentation, such as CVD from primary reflux, obesity, efficiency of the foot and calf muscle pumps, and other conditions. In regard to DVO alone, the severity and the extent of obstruction play a major role.[3] Several papers have reported the clinical signs and symptoms of patients with DVO. Iliofemoral obstruction has the highest association with the development of signs and symptoms *(Figure 2)*. However, it is not always the case as patients with infrainguinal obstruction may also have reflux and other factors that contribute to the severity of clinical presentation. Venous claudication is almost exclusively seen in patients with postthrombotic iliofemoral obstruction.[5] It has also been reported in patients with nonthrombotic obstruction, but this, in our experience, is rare.

The significance of an iliac vein lesion is determined by its impact on blood flow. There may be a flow reduction across the lesion at rest or during physical activity. Collateral veins may often bypass the obstruction. If the collateral veins provide adequate drainage, the patients are asymptomatic. The collateral veins may be adequate at rest but not be enough during physical activity. Patients with DVO can develop signs and symptoms due to ambulatory venous hypertension from inadequate venous return. IVC is a prevalent finding in the general population. Unfortunately, there is no robust diagnostic criteria for defining hemodynamically significant obstruction. In fact, in a study in which 20 healthy individuals were tested for obstruction by venography, 80% (16 out of 20 of the volunteers) had at least 2 venographic signs indicative of IVC.[6] This shows that diagnosis of true iliac vein obstruction is quite challenging. Clearly, the morphologic and hemodynamic changes seen in venography do not translate into disease severity, as all of them were normal individuals. Therefore, it is better to focus on treating the patient based on their symptoms. It is not clear why and when nonthrombotic obstruction leads to symptoms. It may be that with the obstruction getting worse over time, the venous wall becomes less compliant or, in a more obvious case, symptoms arise after development of ipsilateral thrombosis. Furthermore, nonthrombotic stenosis can occur in other areas and not just in the left common iliac vein (CIV). It has been described in the right CIV, in both external iliac veins (EIVs), and in the common femoral vein (CFV). Patients may present with more than one lesion or a combination of nonthrombotic and postthrombotic obstruction. It is important to diagnose all the areas and types of venous obstruction.

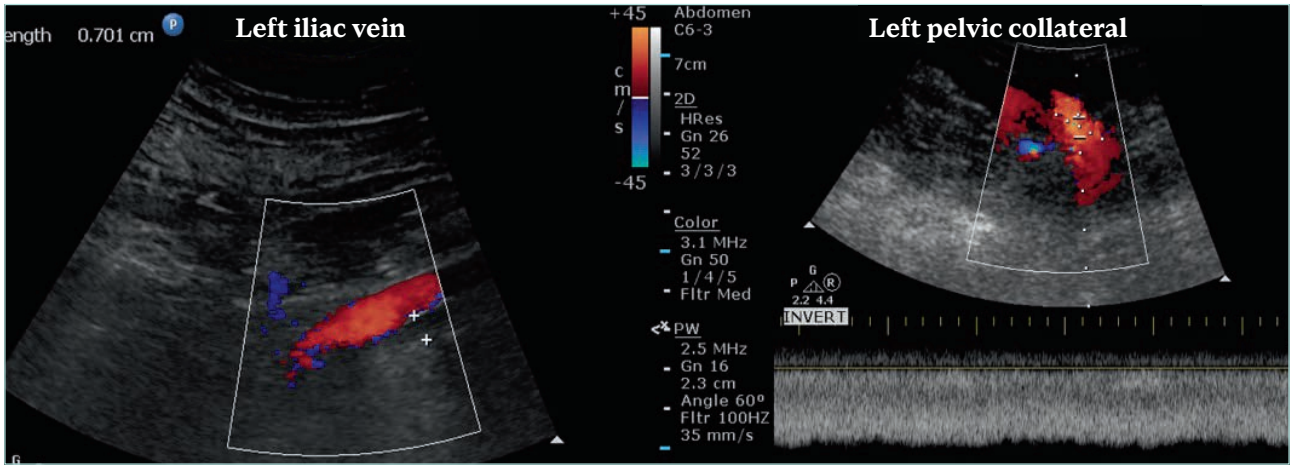

Figure 2. This patient had a chronic postthrombotic occlusion. The patient presented with edema, pain, and skin damage. The left external iliac vein (EIV) was compressed by the left external iliac artery and the patient developed ipsilateral iliofemoral deep venous thrombosis (DVT) leading to skin damage. The left EIV was occluded with the diameter measuring 7 mm. The vein had a focal stenosis prior to DVT but after it retracted throughout its length. The common femoral, femoral, and popliteal veins had partial recanalization with reflux. The ipsilateral common iliac vein (CIV) was patent, receiving flow from the left internal iliac vein. A large pelvic collateral vein (12 mm in diameter) is seen with nonphasic, high-velocity flow. No flow augmentation is seen during thigh compression. Other collateral veins were found connecting to the internal iliac vein.

Diagnosing DVO

There are many ways to diagnose DVO such as ultrasound, intravascular ultrasound (IVUS), venography, computed tomography venography (CTV), and magnetic resonance venography (MRV). Plethysmography has been seen in several

reports, but nowadays is not so common in clinical practice. Vein pressures have been reported but not used routinely.

Typically, DVO can be evaluated through 2 distinct approaches: morphological testing and hemodynamic testing. Morphological testing focuses on visualizing the physical structure of the veins to identify any obstructions. Specific factors such as stenosis, occlusion, length, collaterals, and flow patterns are assessed. However, relying solely on morphological evaluation may lead to incomplete diagnoses or misdiagnoses due to potential discrepancies with real-life conditions. In contrast, hemodynamic testing examines the functional aspects of blood flow within the affected veins, encompassing information about blood pressure, velocity, and flow characteristics. Additionally, the assessment of positional differences and blood flow during rest and exercise is beneficial. Various methods, including plethysmography and measurement of pressure differences, can facilitate hemodynamic testing. Combining information from both types of testing allows health care professionals to perform a comprehensive assessment, facilitating the development of an appropriate treatment plan tailored to the individual patient's condition. This integrated approach ensures a more accurate and holistic evaluation of DVO, enhancing patient care and outcomes.

The current method used routinely in first line for diagnosing DVO morphologically is ultrasound. It is cheap, readily available, and can give both morphologic and dynamic information. Direct and indirect criteria for diagnosing DVO with ultrasound are used, as follows:

Direct criteria

- Planimetric diameter stenosis.
- Peak vein velocity ratio >2.5.
- Luminal changes.

Indirect criteria

- Evaluation of flow patterns of the veins in the groin area and most often the common femoral vein.
  - *Nonphasic flow* at rest and particularly during the Valsalva maneuver.
  - *Low or no velocity augmentation* in CFV during thigh compression or dorsi/plantar flexion.
  - *Asymmetrical flow* pattern between the left and right.
  - *Reversed flow i*n the ipsilateral internal iliac and deep external pudendal veins.
  - *Cephalad flow* in the ipsilateral inferior epigastric vein.

- Presence of collateral veins.
- Difficulty in compressing CFV (high venous pressure).

Although these measures offer valuable information, they also have limitations. Planimetric evaluation relies on vein diameter and area measurements, which can be influenced by image quality, vessel shape irregularities, and operator variability. Noncircular or tortuous veins can also complicate precise measurements. The presence of collaterals, whereas suggestive of chronic obstruction, does not rule out an acute or recent DVO, and some patients may have naturally occurring collaterals. Flow patterns can be impacted by patient positioning and body movement, making it challenging to distinguish true flow alterations from artifacts when relying solely on morphological-based diagnostic tools.

Inflow veins are usually evaluated by ultrasound and venography. The evaluation of inflow veins is crucial for diagnosing DVO. Inflow veins can be evaluated by monitoring the flow velocity and flow patterns. It is very important to evaluate inflow veins before performing any procedures. They can help determine what type of procedure is required. If the inflow veins have little to no flow, stenting would not be the method of choice as the failure rate is high. Evaluating inflow veins is useful but still has some limitations, adding another challenge to diagnosing DVO. Flow rates during venography are not standardized, and values for ultrasound evaluation are not yet established. More work is needed to establish robust criteria for the inflow to improve the management of such patients.

Another challenge with using only morphologic testing such as ultrasound is that individuals with nonthrombotic obstruction have positional stenosis. All routine testing is done in supine position. Postural changes dramatically affect the cross-sectional area of the left CIV and the left renal vein and thus the degree of stenosis in women diagnosed with pelvic venous disorders (*Figure 3A*). Stenosis found in patients while supine often disappears when the position is changed to lying on the left side or to standing.[7] Symptoms of venous obstruction are present and more pronounced during physical activity. This is important to consider because therapeutic decisions made when patients are in a supine position are more likely to be ineffective. We should identify patients with a fixed stenosis and appropriate symptoms *(Figure 3B)*. Patients with postthrombotic obstructions typically do not experience positional stenosis. The obstruction is longer and most often there is intraluminal material. In few cases (work in progress) patients with nonthrombotic stenosis who develop DVT may have positional changes or the lesion can become fixed due to postthrombotic changes.

IVUS is very useful in making accurate diagnoses as it is inside the vein and offers 360-degree views. It is best to characterize the stenosis, wall, and intraluminal changes. It is also used to guide procedures and offer immediate results on the effect of interventions. In nonthrombotic patients, it was shown that a threshold of >61% of diameter stenosis by IVUS may better predict clinical improvement.[8] Positioning of the patient can also be an issue in making an accurate diagnosis. However, performing the Valsalva maneuver and hydrating the patient well improves the diagnosis.

Axial imaging with CTV and MRV using appropriate protocols provides accurate imaging and offers great differential diagnosis. The large field of view, 3D reconstructions, and intravascular and extravascular images are advantages of these methods. MRV can also provide dynamic flow that can help in determining the hemodynamic patterns. Positioning, motion artifacts, metallic structures, and poor hydration can pose significant problems for accurate diagnosis. It has been demonstrated that placing the patient in a prone position may overcome the positional stenosis.[9]

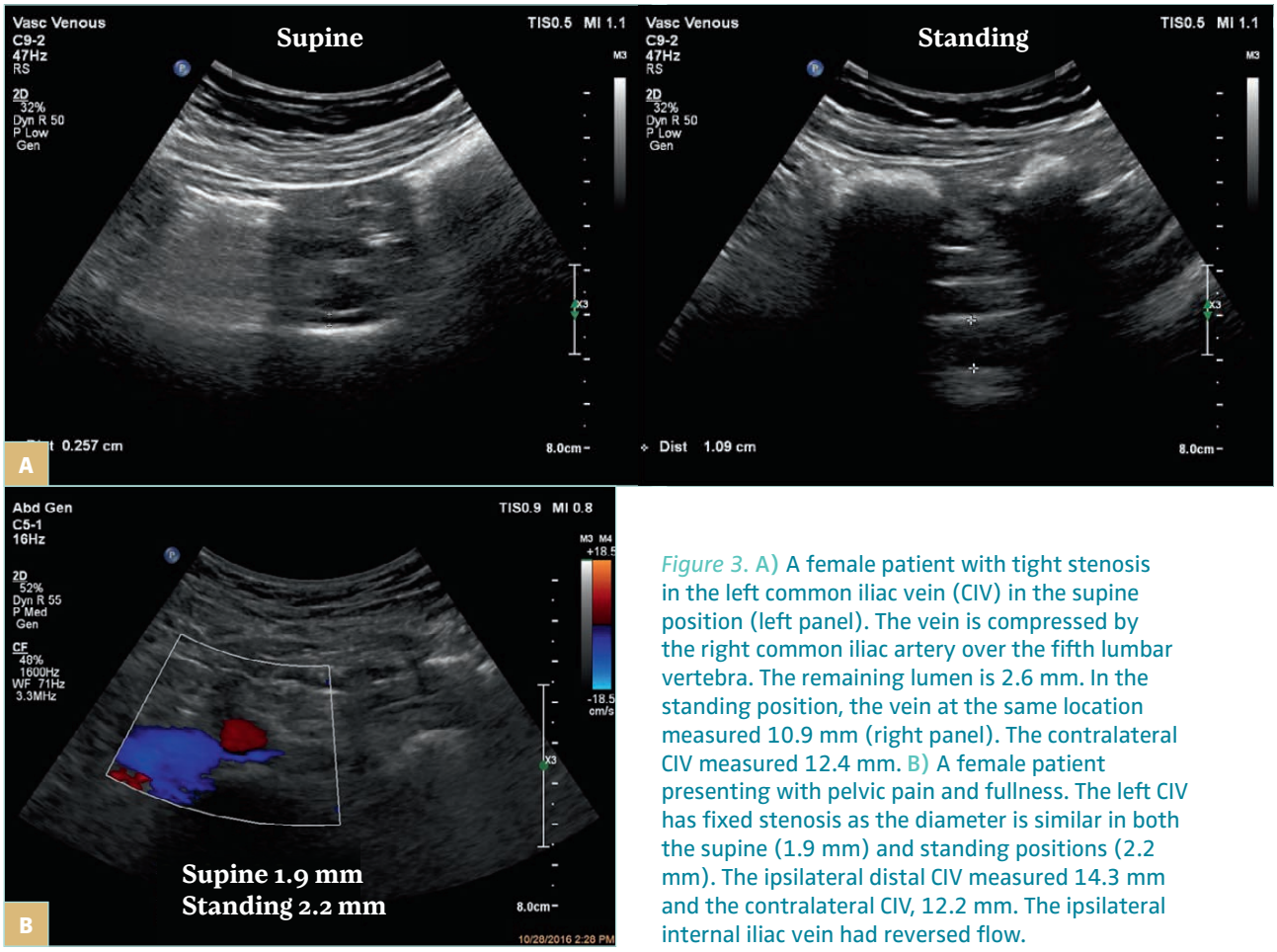

Figure 3. A) A female patient with tight stenosis in the left common iliac vein (CIV) in the supine position (left panel). The vein is compressed by the right common iliac artery over the fifth lumbar vertebra. The remaining lumen is 2.6 mm. In the standing position, the vein at the same location measured 10.9 mm (right panel). The contralateral CIV measured 12.4 mm. B) A female patient presenting with pelvic pain and fullness. The left CIV has fixed stenosis as the diameter is similar in both the supine (1.9 mm) and standing positions (2.2 mm). The ipsilateral distal CIV measured 14.3 mm and the contralateral CIV, 12.2 mm. The ipsilateral internal iliac vein had reversed flow.

Venography is used most often in treatment. It offers both morphologic and dynamic information. It is a good method that provides a large field of view and flow patterns in the areas of obstruction, collaterals, and inflow veins. It's not as good as IVUS for characterizing the severity of the obstruction and luminal changes, and it also cannot be used to visualize the wall and extraluminal structures. Thus, it is often used together with IVUS. Similarly with the other methods, venography is performed in the supine position and has issues with positional stenosis. Venography can be misleading as shown by van Vuren et al,[6] and it can over- and underestimate the disease.

One of the ways we can overcome some of the limitations of morphologic testing alone is by combining the strengths of different methods. By integrating morphologic testing, we gain precise insights into the obstruction's shape and dimensions. Simultaneously, employing hemodynamic tools empowers us to assess the obstruction's impact on blood flow dynamics, completing a comprehensive picture of the condition.

In many patients, the symptoms become more apparent during exercise, and therefore hemodynamic evaluation before and after exercise provides valuable insights. In a study involving 50 patients with postthrombotic disease, venography and bilateral femoral vein pressure measurements were carried out. The severity of the obstruction was best evaluated by observing the pressure elevation and difference after exercise and the time required for the parameters to return to baseline. Interestingly, after exercising, 12 out of the 50 patients showed pressure changes like those with normal iliac veins, indicating improved blood flow and less-severe obstructions. Their pressures returned to pre-exercise levels within 20 seconds. In this instance, phlebography played a morphological role, whereas femoral vein pressure measurements provided clinically significant information before and after exercise for postthrombotic iliac vein disease.[10] The use of pressure measurements completes the picture and may provide better guidance for treating patients. The presence of a venous pressure gradient increases the confidence for performing an intervention. The absence of pressure gradient cannot always exclude the contribution of obstruction in the occurrence and severity of signs and symptoms.

These findings underscore that relying solely on venography would not be sufficient to accurately assess the severity of obstructions in patients with postthrombotic disease. A comprehensive evaluation is essential to gain a complete understanding of each patient's condition. Different patients may exhibit varying degrees of blood flow improvement, which could influence treatment decisions. Some patients might require less aggressive interventions, whereas others may need more intensive treatments to manage their condition effectively. Moreover, using invasive pressure measurements as a stand-alone diagnostic tool may not always be indicative of a DVO diagnosis. Therefore, a hemodynamic diagnostic approach should not be used in isolation, and integrating

both hemodynamic and morphologic evaluation ensures a more comprehensive and accurate assessment of thrombosis or obstruction. Patients with CVD symptoms and signs where both morphologic and hemodynamic assessment are associated with the clinical presentation are the best candidates for intervention. However, patients may still have signs and symptoms without hemodynamic changes. In absence of anything else, such patients may benefit from treatment, but this needs to be further studied.

Finally, current diagnostic tests need to be optimized and improved criteria need to be developed for DVO diagnosis. Since signs and symptoms are more apparent during physical activity, tests need to be modified at least in those patients where the contribution of obstruction is not clear. Together with advances in DVO diagnosis, the findings need to be considered in context with the clinical presentation, other contributing factors, and history of the patients.

Conclusion

To address challenges for DVO diagnosis and improve patient outcomes, it is imperative to adopt a more comprehensive diagnostic approach. Presently, the standard diagnostic method primarily relies on only morphologic testing; however, this approach may not provide a complete understanding of the obstruction and its characteristics. Thus, it is necessary to improve by incorporating both morphologic and hemodynamic tests when an obstruction is suspected. By combining these diagnostic modalities, clinicians can gain comprehensive insights into the nature of the obstruction, enabling them to develop more personalized and effective treatment plans. Further work is needed to develop more rigorous tests and robust criteria for optimizing the care of patients with DVO.

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Progress in the management of early thrombus removal

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ABSTRACT

Deep venous thrombosis (DVT) is common and can be a source of morbidity by way of short-term disabling symptomatology and mid-long-term postthrombotic syndrome (PTS). Randomized trials and prospective studies have demonstrated both early and late symptomatic benefit in early recanalization of the iliocaval system of selected patients. On the basis of emerging evidence, published guidelines recommend early thrombus removal in iliofemoral DVT in symptomatic good-risk patients. In light of these recommendations, catheter-directed thrombolysis (CDT) and/or mechanical thrombectomy (MT) have become more popular among vein specialists. This review article summarizes current evidence, novel technologies, and the technical approach to the management of iliofemoral DVT.

Keywords

acute deep vein thrombosis | intravascular ultrasound | mechanical thrombectomy | postthrombotic syndrome | thrombolysis | venous stent

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Introduction

Over the past 15 years, interventional therapies targeting early thrombus removal have evolved as a potentially better alternative for good-risk patients with iliofemoral deep venous thrombosis (DVT), aiming to decrease postthrombotic syndrome (PTS) rates or severity and improve quality of life (QOL). DVT intervention has steadily migrated toward more minimally invasive techniques in the form of catheter-directed thrombolysis (CDT) and mechanical thrombectomy (MT). Whereas indications and appropriate patient selection are still an area of controversy, increasing awareness, mounting evidence, and experience have earned these modalities a favored place in iliofemoral DVT management.

What have we learned from the lytic trials?

CDT—from early observational cohort studies, comparative nonrandomized, and small randomized studies—appeared to be associated with increased vein patency, valve preservation, and a reduction in the incidence of PTS compared with conventional anticoagulation therapy alone.[1-4]

The first large, randomized trial was the Norwegian CaVenT trial (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis). The investigators recruited 209 patients, half of them with an iliofemoral DVT.[5] Patients were randomized to standard anticoagulation alone or CDT plus anticoagulation. At 24 months, PTS (Villalta score ≥5) developed in 41% of patients in the CDT group and 56% of patients in the standard anticoagulation therapy group (P=0.047). Of note, major bleeding events during the index hospitalization occurred in 2.9% of patients. No bleeding events occurred in the anticoagulation-alone group. At 5 years, the rates of PTS were 43% in the CDT group and 71% (P<0.0001) in the control group. No difference was found in QOL.[6]

The ATTRACT trial (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis), the largest randomized controlled trial (RCT) to date involved 691 patients with iliofemoral or femoropopliteal DVT.[7] They were randomized to standard anticoagulation therapy alone or pharmacomechanical thrombolysis (PMT) plus anticoagulation. PMT involved predominately the use of the AngioJet device (Boston Scientific Corporation, Marlborough, Massachusetts, USA). At 24 months, PTS (Villalta score ≥5) was 47% in the CDT group and 48% in the anticoagulation-alone (control) group (P=0.56) indicating no benefit for an intervention. Again, bleeding events were more frequent in the procedural group (1.7% vs 0.3%) although none was cerebral or life threatening. A subgroup analysis of the 311 patients with iliofemoral DVT demonstrated that moderate or severe PTS (Villalta score ≥10) was present in 18% in the CDT group and 28% in the anticoagulation group (P=0.021) and severe PTS (Villalta score ≥15) was present in 8.7% in the PMT group and 15% in the anticoagulation group (P=0.048).[8] At 30 days, the mean reduction in pain score from baseline was -2.36 in the PMT group and -1.80 in the anticoagulation group (P=0.0082). Mean QOL score at 24 months was 21.5 in the PMT group and 16.2 in the anticoagulation group (P=0.043). Although the primary end point in the ATTRACT trial was not reached, in patients with iliofemoral DVT, PMT resulted in reduction in PTS of any severity using the venous clinical severity score (VCSS), reduction in moderate or severe PTS, reduction in pain and swelling, and improved disease-specific QOL.[8-10]

The most recent randomized study is the Dutch CAVA trial (CAtheter Versus Anticoagulation alone for acute primary [ilio] femoral DVT), which compared ultrasound-accelerated CDT (EKOS, Boston Scientific Corporation) against anticoagulation for acute iliofemoral DVT.[11] This trial recruited 162 patients. Major bleeding occurred in 5% of patients in the CDT group, and no bleeding in the control group. At 12 months, there was no statistical difference in PTS (Villalta score ≥5) between groups: it occurred in 29% of patients in the interventional group and 35% in the anticoagulation alone group (P=0.42). However, a difference in PTS incidence was shown after a median follow-up of 39 months, with reported rates being 47% in the intervention group versus 69% in the group with standard therapy (P=0.01). This difference was the result of a significantly higher number of new diagnoses of mild PTS at the final follow-up visit in the anticoagulation group. For neither definition of PTS was a clinically meaningful change in any of the patient-reported QOL scores demonstrated.[12]

The conflicting results of the existing RCTs have raised criticism mainly toward diverse patient inclusion criteria or technical variations (eg, stenting rates, timing of intervention, inflow optimization, etc).[9,10,13] However, there is little doubt that these trials demonstrated that a certain population can benefit in terms of PTS severity reduction and QOL improvement, and this benefit extends beyond 2 years after treatment.[9,10-14] The lytic trials confirmed this benefit in good-risk symptomatic patients with iliofemoral DVT, provided intervention is done early enough, ideally within a 2-week window.[13,14] Based on these data, the European Society of Vascular Surgery in its most recent guidelines is recommending early thrombus removal strategies in selected symptomatic patients with iliofemoral DVT (Level of evidence A, recommendation class IIa [evidence in favor of efficacy]).[15]

We need to acknowledge though that CDT has been associated with higher rates of blood transfusion, pulmonary embolism (PE), bleeding events, and vena cava filter placement. In some

countries, CDT is also associated with longer hospital stays and 3 times the hospital costs.[16] These are conclusions that have all derived from the lytic trials; however, contemporary practice is shifting away from pure CDT techniques and, without abandoning it, MT is inevitably rising.

Thrombolytics delivered through standard multi-sidehole catheters or in the form of ultrasound-accelerated thrombolysis (EKOS System), for the patient who has minimal bleeding risk, still remain relevant and essential in certain cases as follows: i) to establish inflow in an ''ascending'' thrombosis (eg, patient with iliofemoral and tibial/popliteal DVT); ii) in any patient whose collateral iliocaval flow is thrombosed and vital to be established (eg, inferior vena cava aplasia); iii) in-stent thrombosis; iv) in inferior vena cava (IVC) filter thrombosis; or v) in extensive bilateral DVT to debulk the large amount of fresh thrombus before initiating MT. It should also be noted that thrombolytics can always bail out an unsuccessful MT procedure as well as an MT procedure can bail out an unsuccessful CDT.

Shifting toward mechanical thrombectomy

Over the past 5 years, contemporary thrombectomy techniques have evolved toward thrombolytic free interventions, altering the safety profile and the complex hospital logistics (eg, need for intensive care unit [ICU] stay). Current practice has shifted toward MT, with a single-session treatment with no ICU stay. Multiple thrombectomy devices are available in the market, but an individual analysis of each one of them is beyond the scope of this document *(Figure 1)*.[17-21]

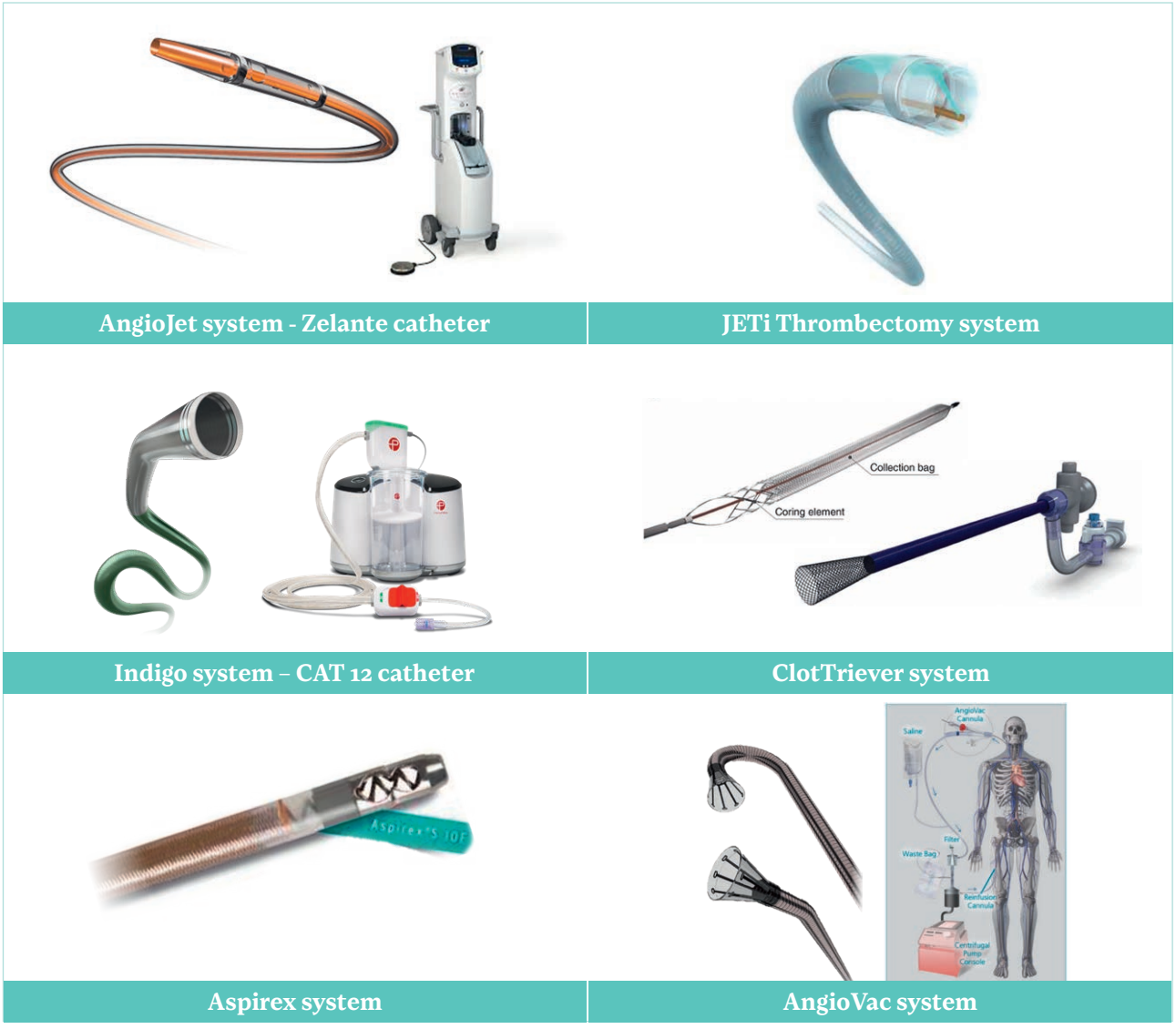

Figure 1. Contemporary mechanical thrombectomy devices: AngioJet (Boston Scientific Corporation), ClotTriever (Inari Medical), JETi (Abbott), Aspirex (BD Medical), Indigo CAT 12 (Penumbra), AngioVac (AngioDynamics).

There is mounting evidence from ongoing registries and institutional series on their safety and effectiveness, but there is no long-term (>2 years) data on PTS prevention and no comparative analysis against anticoagulation. Of note, the first RCT was recently initiated, and it is industry sponsored by Inari Medical (DEFIANCE: RCT of ClotTriever System Versus Anticoagulation in Deep Vein Thrombosis).[22] This RCT will enroll 300 patients from up to 60 centers worldwide to compare MT with anticoagulation alone for the treatment of iliofemoral DVT. The primary end point for the trial is a hierarchical composite of treatment failure and PTS syndrome severity at 6 months.

Technical aspects for optimal outcomes

Before the decision to intervene, thrombus within the iliofemoral segment needs to be confirmed. Aside from a baseline duplex scan, a cross sectional imaging MR venogram or computed tomography (CT) venogram (abdomen, pelvis, and upper leg) can facilitate operative planning by documenting the extent of the thrombus and uncovering unusual anatomies (eg, duplicated cava, IVC aplasia, etc) or chronic venous obstruction. Decision-making and technique selection are summarized in *Figure 2*.

Access

With few exceptions, treating an iliofemoral DVT will require popliteal vein access with the patient in prone positioning. This will guarantee good control and imaging of the femoral bifurcation that is the gatekeeper of iliac vein patency. The presence of popliteal thrombus is not a contraindication to access the vein. Use of ultrasound and a micropuncture system is recommended to minimize bleeding complications, particularly if CDT is considered. If needed, the popliteal vein can accept large sheaths to accommodate the standard venous stent delivery systems (9 or 10 Fr) and even up to 16 Fr after serial dilatations for larger thrombectomy devices. Proximal tibial or small saphenous access can also be obtained and can accommodate 9- to 10-Fr sheaths. An ipsilateral mid-femoral puncture in the supine position can also be sufficient for isolated iliac or caval DVT.

A 5-Fr short sheath, a starter 0.035-inch wire, and a standard guiding catheter are typically enough to cross fresh thrombus and obtain images at the femoropopliteal and iliocaval segments.

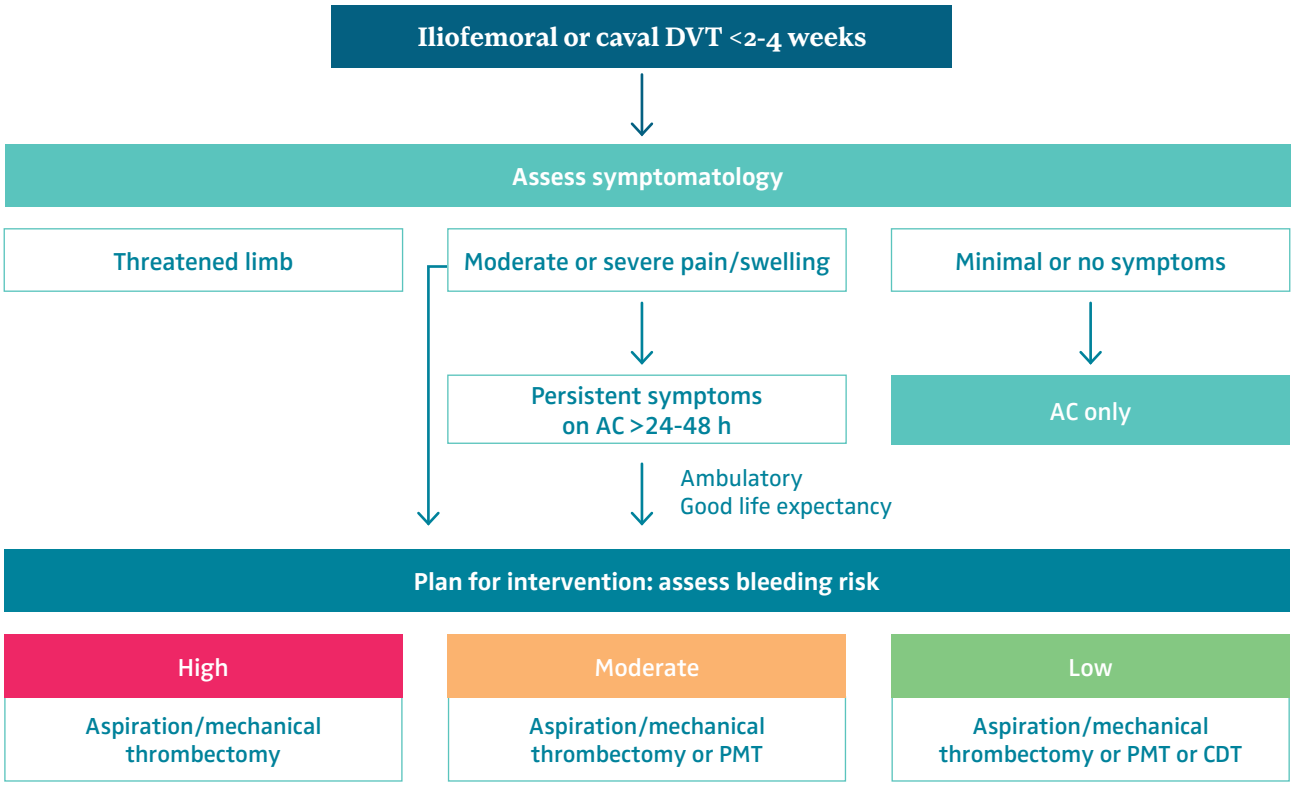

Figure 2. Patient and treatment selection for iliofemoral deep venous thrombosis.

Abbreviations: AC, anticoagulation; CDT, catheter-directed thrombolysis; DVT, deep venous thrombosis; PMT, pharmacomechanical thrombectomy.

Thrombolysis, thrombectomy, and IVC filters

Thrombolysis can be performed using a multi-sidehole standard catheter or the EKOS catheter that incorporates ultrasound probes to accelerate fibrin separation. It is essential to accommodate the entire infusion catheter segment (available is several lengths 5-50 cm) within the clot; otherwise, the lytic agent will escape through the holes of least resistance into the blood stream and not within the clot. Contemporary thrombolysis protocols can vary in time between 6 to 12 hours, and dosage should typically range between 0.5 to 2 mg/hour. Patients will need to be transferred to the intensive care unit for monitoring during the dripping and returned to the interventional suite for termination of the procedure. Frequently, extension of CDT up to 48 hours or additional MT may be required to maximize clot removal.

Aspiration or MT can be performed with any of the novel available devices on the market *(Figure 1)* with which the practitioner feels comfortable. A 10- to 16-Fr sheath will typically be required. The ultimate target of a successful thrombus removal is >90% extraction and provides optimal inflow (through the femoral and deep femoral veins) to the iliac segment. This will minimize the risk of early re-thrombosis or later PTS.[23-26]

Regarding the use of IVC filters, whereas a small, randomized trial has indicated a higher rate of clinically significant PE in patients not receiving one, there was no mortality difference, and subsequent contemporary studies recommend highly selective IVC filtration.[27] PE can be unavoidable, but they are rarely clinically meaningful for otherwise good-risk patients, and placement of an IVC filter may introduce complexity and other potential risks. Patients that might benefit are those with associated PE on presentation, with large mobile thrombus, or those who are planned for aggressive pharmacomechanical thrombectomy involving the IVC.[28]

Intravascular ultrasound

Intravascular ultrasound (IVUS) allows for detailed images acquired in an axial plane relative to the catheter tip; it reduces radiation exposure and contrast volume in the typically young patient. IVUS has been shown in multiple studies to be superior for accurate lesion identification compared with plain venography, and its use improves long-term patency.[29] In contemporary acute DVT intervention, IVUS is essential not only to identify residual clot and external compression but also to guide choice of stent diameter and landing zones, and to confirm a satisfactory final outcome (eg, stent expansion).

Additionally, distance markers on the catheter shaft can be used for precise length measurements. If IVUS is not available, multiple venographic projections should be obtained for lesion identification.

Venous stents

Several dedicated venous stents are available *(Figure 3)*. Sufficient stenting of persistent lesions (chronic obstruction, residual thrombus, external compression) following thrombus removal seems to be a critical component of a clinically successful procedure *(Figure 4)*. Accumulated experience favors liberal stenting and use of dedicated venous stents to ensure good inflow and outflow. Consequently, in many cases it may be necessary to stent from the iliocaval confluence down to the common femoral vein.[25] Care should be taken to prevent jailing of contralateral common iliac vein as well as jailing of the deep femoral vein when extending distally. The common iliac vein is typically stented with a 14- to 16-mm stent, and the external iliac/common femoral veins with a 12- to 14-mm stent. The length of the iliac stent should also be long enough (≥8 cm) to anchor at the external iliac segment, preventing migration and avoiding an acute angulated landing at the iliosacral curvature.

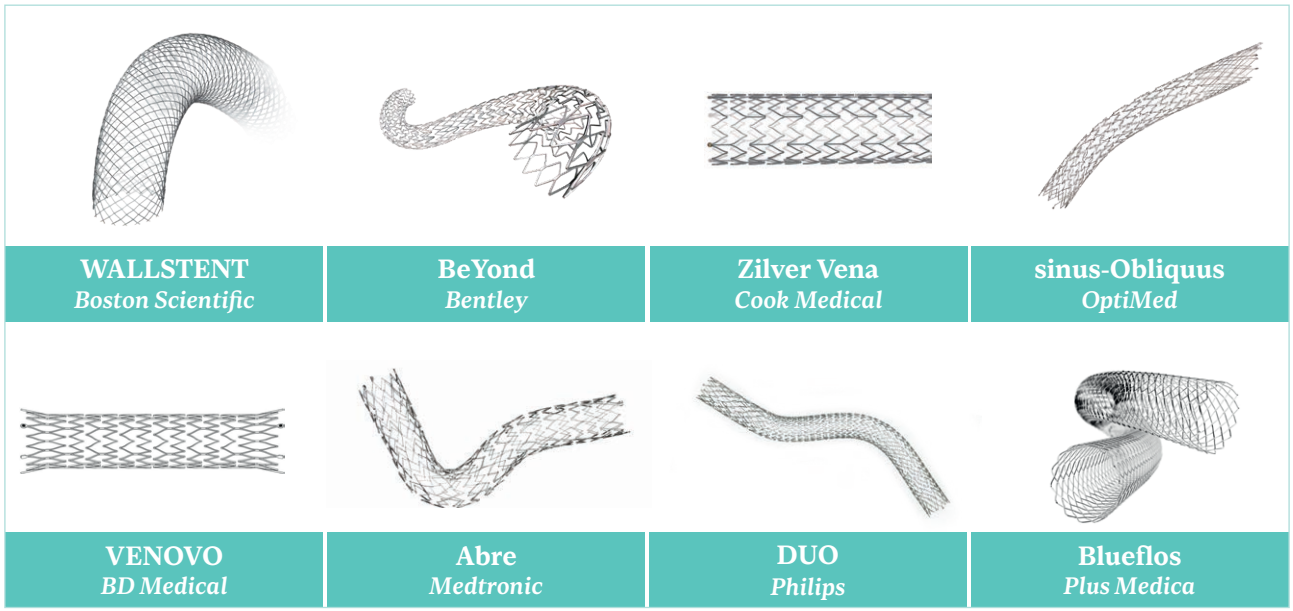

Figure 3. Dedicated venous stents available on the European market.

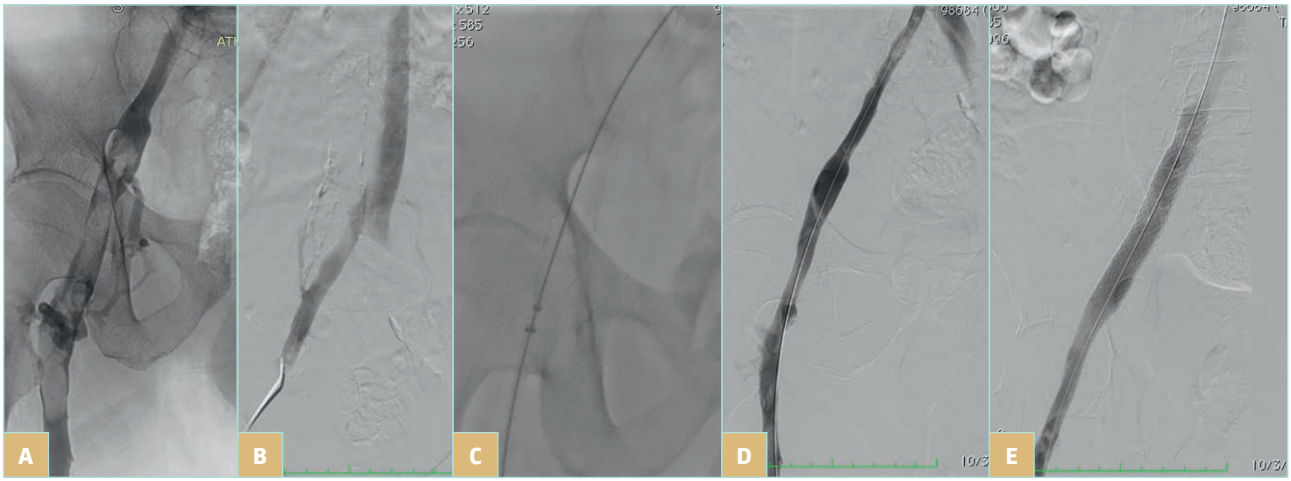

Figure 4. Symptomatic iliofemoral deep venous thrombosis (DVT) managed with ClotTriever (Inari Medical) mechanical thrombectomy and placement of a 14x 100 m BeYond (Bentley) stent: A) thrombus at the iliofemoral segment extending distally to the origins of the femoral and deep femoral veins; B) clean but diseased proximal iliac segment (notice the presence of collateral vein); C) mechanical thrombectomy (notice the coring element and the collection bag of the ClotTriever device); D) venogram post thrombectomy with almost complete thrombus resolution but residual stenosis (confirmed also with intravascular ultrasound); and E) final venogram after stent placement indicating brisk flow through the previously thrombosed iliofemoral segment.

Perioperative care and surveillance

The patient should remain on bed rest for 2 to 4 hours to allow for hemostasis; the index leg needs to be tightly wrapped, and after hospital discharge, thigh-high compression at 20 to 30 mm Hg should be encouraged for at least 1 month or until the swelling completely resolves. The patient should also be encouraged to drink plenty of fluids in order to minimize the effects of hemoglobinuria. Within 6 to 8 hours, the patient should be encouraged to ambulate.

The patient should be discharged with a defined plan for anticoagulant therapy that is consistent with their risk of recurrence.[15,30] For patients who received a stent, before initiating oral anticoagulation, low molecular weight heparin for 2 to 6 weeks is preferred owing to its anti-inflammatory effects. An antiplatelet agent for 6 months or indefinitely depending on the patient's risk profile can be considered. Appropriate referral to hematology is warranted in patients with an unprovoked DVT or possible thrombophilia. A follow-up office visit is recommended at 2 to 4 weeks, at 3, 6, and12 months, and annually thereafter with duplex ultrasound.[15,30,31] Cross-sectional imaging can be needed on occasion in complex iliocaval reconstructions to evaluate patency.

Conclusions

Mounting evidence demonstrates early symptomatic relief and PTS severity reduction with early percutaneous DVT debulking. Although anticoagulation and compression remain the mainstay of treatment, patients with iliofemoral DVT associated with swelling and pain, and good life expectancy, should be strongly considered for treatment with a minimal invasive catheter intervention. Contemporary procedures are generally safe and do not require prolonged hospitalization. As DVT rates are rising, awareness of novel treatments and appropriate technical expertise within a multidisciplinary team can guarantee optimal results and ultimately a better QOL for our patients.

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Management of chronic deep venous obstructive disease

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ABSTRACT

Chronic deep venous obstructive disease occurs in both the lower and upper extremities. Although they share similar features, particularly with respect to pathophysiologic changes associated with postthrombotic obstruction, they are clinically and epidemiologically distinct processes. As a result, there are significant differences in disease course, clinical approach, and management. While conservative measures, including elastic compression, remain the mainstay for symptom management, endovascular treatment of obstruction has become a vital approach for persistent, debilitating symptoms in both entities. Permanent stent placement remains far more common in lower-extremity obstruction due to iliofemoral/iliocaval outflow obstruction. By contrast, upper extremity obstruction frequently requires adjunctive open surgical approaches, most commonly in the setting of venous thoracic outlet syndrome, whereas open surgery is less common in lower-extremity disease and can include endophlebectomy of the common femoral vein and venovenous bypass for iliac/caval obstruction. In this chapter, the epidemiology, clinical course, and endovascular management of upper- and lower-extremity venous obstructive disease will be reviewed.

Keywords

lower-extremity deep venous occlusive disease

nonthrombotic iliac vein lesions

thoracic central venous obstruction

upper-extremity deep venous occlusive disease

post-thrombotic syndrome

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Introduction

Chronic lower-extremity deep venous disease

Lower-extremity deep venous occlusive disease is most commonly separated into postthrombotic and nonthrombotic etiologies. Postthrombotic syndrome (PTS) occurs with varying severity in approximately 50% of all patients after lower-extremity acute deep venous thrombosis (DVT).[1] Involvement of the iliofemoral (common femoral, external iliac, and common iliac) venous segments and inferior vena cava (IVC) are frequently associated with more severe PTS symptoms, which can include pain/fatigue, severe edema, dermatitis, and soft tissue ulceration.[2,3] The pathophysiology of PTS consists of a combination of luminal obstruction from organization of thrombus into type 3 and type 1 collagen, as well as inflammation that damages venous valves leading to reflux; together, they clinically result in ambulatory venous hypertension.[4] Treatment of PTS is via both medical and interventional means. Elastic compression stockings (ECS) have not been shown to prevent development of PTS[5]; however, it is accepted as an important adjunct in symptom management and improvement in quality of life.[6] Supervised exercise programs and venoactive medications, when tolerated, also play a role. Postthrombotic obstruction can be treated via the endovascular placement of self-expanding venous stents, which can reduce pain, edema, and promote ulcer healing.[7] Treatment of superficial reflux is also an important component in the management of PTS.[8]

Nonthrombotic venous obstruction is most commonly caused by external compression of deep veins by arteries. Left iliac vein compression syndrome (frequently referred to as ''May-Thurner syndrome'') is the most commonly encountered type, where there is compression of the left common iliac vein between the right common iliac artery and vertebral body; various other compression phenomena can occur, including obstruction of the external iliac vein by the ipsilateral external iliac artery. Although compression syndromes can result in acute iliofemoral DVT, they can also cause venous stasis symptoms in the absence of thrombus, including pain/fatigue, edema, ulceration, and in females, symptoms of female pelvic venous disease (commonly known as pelvic congestion syndrome); such lesions are commonly referred to as nonthrombotic iliac vein lesions (NIVLs). However, accurate estimation of the incidence of clinically significant NIVLs is difficult as they can nonpathologically present in a significant portion of the population and are asymptomatic[9]; thus, a thorough clinical evaluation to exclude other causes is mandatory prior to intervention. Self-expanding venous stents can be placed when treatment is indicated. Finally, extrinsic venous compression associated with adjacent malignancy can occur, and is variably associated with thrombosis of the impacted segment and inflow veins.

Chronic upper-extremity deep venous disease/thoracic central venous obstruction

Unlike lower-extremity venous obstruction, upper-extremity deep venous disease resulting from thoracic central venous obstruction (TCVO) can result from several different etiologies, including indwelling central venous devices, extrinsic compression from musculoskeletal compression or malignancy, and infectious/inflammatory processes. Anatomic compression of the subclavian vein between the first rib/clavicle or anterior scalene muscle/subclavius muscle/first rib can result in chronic occlusion typical of venous thoracic outlet syndrome (vTOS); when there is associated acute axillosubclavian DVT, this is also known as ''Paget-Schroetter syndrome.'' This entity is most commonly seen with repetitive motions, such as those seen in athletes.

Given the myriad causes and the variety of anatomy that can be affected by TCVO, the epidemiology remains poorly understood; similarly, the clinical course and management can vary significantly.[10] Patients can present with severe symptoms such as pain, facial edema, and respiratory distress resulting from superior vena cava (SVC) syndrome or can be relatively asymptomatic. Thus, an individualized approach is necessary to effectively manage patients with TCVO.

Indications for intervention

Postthrombotic lower-extremity deep venous obstruction

Patients with moderate-to-severe PTS have a history of DVT in the index limb and most frequently have a component of iliofemoral and/or iliocaval venous occlusion/obstruction on noninvasive imaging studies. Patients can have the numerous symptoms/findings to varying degrees; endovascular recanalization therapy is typically considered when symptoms persist despite conservative therapy including elastic compression and venoactive medications. Patients typically have symptoms that classify as C3-C6 disease by the clinical, etiologic, anatomic, pathologic (CEAP) scale; Villalta scores of 10 or greater/ venous clinical severity scores (VCSS) of 8 or greater are most frequently encountered. Patients can experience pain that limits or prevents normal activities of daily living and worsens with short periods of activity or standing or during walking (venous claudication). Edema is frequently present and involves the calf and thigh. Skin damage of the affected

limb is common and can include eczema, subcutaneous fibrosis, lipodermatosclerosis, and/or atrophie blanche. The most severe manifestation of PTS is venous stasis ulceration, which is frequently present around the malleoli and pretibial soft tissues.

Nonthrombotic lower-extremity deep venous obstruction

Patients with NIVL may present with symptoms that include asymmetric lower-extremity edema, pain, heaviness, and/or fatigue of the affected extremity with activity or prolonged standing or during walking (venous claudication), and asymmetrically advanced superficial venous disease in the affected limb that may include venous stasis ulceration. Unlike PTS, patients with NIVL may have less than C3 disease, however, in such patients a significant portion of their symptoms must be lifestyle limiting venous claudication. In females, pelvic symptoms may occur, including pain with prolonged periods of standing and with intercourse, and also bladder symptoms. Patients with NIVL, by definition, have no known history of antecedent DVT.

Thoracic central venous obstruction

Symptoms of TCVO are highly variable and depend on the anatomical segment involved, causative factors, and comorbidities. SVC syndrome is most commonly secondary to malignant compression, though can be due to device- or catheter-related occlusion as well as infectious/inflammatory processes (eg, fibrosing mediastinitis). Patients can present with respiratory distress, severe facial/upper extremity edema, and inability to tolerate oral secretions. Note, no objective symptom grading scale for thoracic central venous occlusions is present. Urgent endovascular intervention and/or external radiation therapy is frequently indicated in these settings. However, patients are frequently minimally symptomatic, such as for dialysis patients with catheter-induced TCVO.

vTOS is due to extrinsic compression of the subclavian vein by a cervical rib or muscular hypertrophy. When DVT occurs in this setting, this is known as Paget-Schroetter syndrome or ''effort-induced'' thrombosis and is frequently seen in athletes. Patients may present with sudden onset, unilateral upper-extremity edema.

Contraindications to intervention

The primary absolute contraindication to intervention, particularly for PTS and vTOS, is an absolute contraindication to anticoagulation. Such patients require durable anticoagulation therapy for intervention to be successful. Other absolute contraindications include active systemic infection, uncorrectable coagulopathy, severe contrast reaction refractory to steroid and antihistamine medications, current pregnancy, known severe allergies to stent material (eg, nickel allergy) and non–dialysis-dependent oliguria where contrast nephropathy is a concern; alternatively, carbon dioxide contrast or IVUS can be used based on operator experience.

Relative contraindications to intervention include anemia, likelihood of low benefit for intervention (eg, minimally symptomatic nonambulatory patients) and short life expectancy; palliative treatment of SVC syndrome can be considered in appropriate procedural candidates.

Preprocedure preparation

Postthrombotic lower-extremity deep venous obstruction

As with all venous disease, a thorough history and physical examination should be obtained, with attention to venous thromboembolism history, including prior episodes of acute DVT. Use and compliance with conservative measures, including compression stockings, venous return assist devices, and venoactive medications should be documented. A complete knowledge of the patient's anticoagulation history is vital; assess for potential risk factors for bleeding from anticoagulation and expected level of patient compliance.

If patients are unlikely to derive benefit from PTS symptom reduction, intervention may not be indicated. For example, selection of patients that are nonambulatory or have a limited life expectancy may not be appropriate candidates for intervention. Thus, it is important to assess for comorbid conditions that may impact the success or safety of an intervention. Furthermore, many PTS patients have phlebolymphedema, which is chronic lymphatic damage that results from chronic venous obstruction and does not typically improve following endovascular intervention; in such cases, counseling and setting appropriate expectations for improvement are key.

Obtain index limb measurements for comparative purposes following intervention. Typically, measure ankle circumference 5 cm above the medial malleolus, calf circumference 5 cm below the tibial tubercle, and thigh measurement above the

patella. If a prior or current venous stasis ulcer is present, assess length of time it was or has been present. If an active ulcer is present, obtain measurements of the ulcer and assess for infection. If infected, prescribe appropriate antibiotic therapy. If involving muscular, tendinous, or osseous structures, obtain wound care/surgical consultation for further management.

Evaluate patients according to venous disease scoring systems to guide decision-making. This includes the CEAP score, VCSS, and Villalta score.

Review noninvasive imaging studies. Evaluate abdominopelvic venous structures with computed tomographic or magnetic resonance venography (CTV or MRV, respectively), or IVC/iliac duplex ultrasonography. The choice of imaging study will be dependent on local practice/physician preference and expertise. Assess for presence of >50% luminal stenosis or occlusion, length of stenosis, and predisposing factors that resulted in occlusion (eg, left iliac vein compression, or in an iliocaval occlusion, an obstructed IVC filter). Inflow assessment is vital to promote stent patency; assess venous inflow at the level of common femoral vein (CFV) with venous duplex ultrasound. If the CFV is occluded or severely stenotic, assess the femoral vein and profunda femoris vein (PFV) for flow and stenosis. The PFV in particular is critical in maintenance of stent patency in the absence of a normal CFV. Evaluate superficial veins for reflux as they may require treatment after successful deep venous recanalization. In patients with stasis ulceration, foam sclerotherapy of the ulcer bed is frequently necessary.

In patients undergoing recanalization, initiate anticoagulation prior to the procedure to ensure tolerance and compliance. In the periprocedural and immediate postprocedural period, low molecular weight heparin (LMWH) is preferred by many due to consistent antithrombotic activity and theoretical anti-inflammatory properties. Anticoagulation is generally continued through the procedure.

Nonthrombotic lower-extremity deep venous obstruction

Obtain a thorough history and physical examination, focusing on venous disease–specific symptoms. Specifically, assess whether superficial venous disease workup and treatment has occurred, as well as trials of conservative therapy (eg, ECS). Given that asymptomatic patients frequently have compressions, it is important to assess for alternative explanations for symptoms. For example, lower-extremity edema can be caused by numerous disorders, including lymphedema, heart failure, hypoalbuminemia, and various medications including calcium channel blockers.

Similar to postthrombotic occlusions, imaging for venous compression is important in preprocedural planning. CTV/MRV and/or IVC/iliac duplex ultrasound are useful to assess for venous compression syndromes. On duplex ultrasound, the presence of ipsilateral internal iliac vein flow reversal may increase confidence that the compression is hemodynamically significant and therefore the cause of the patient's symptoms. Similarly, a duplex ultrasound insufficiency on examination to assess for the presence of deep venous reflux (typically, >1 second) or nonphasic flow adds to diagnostic confidence.

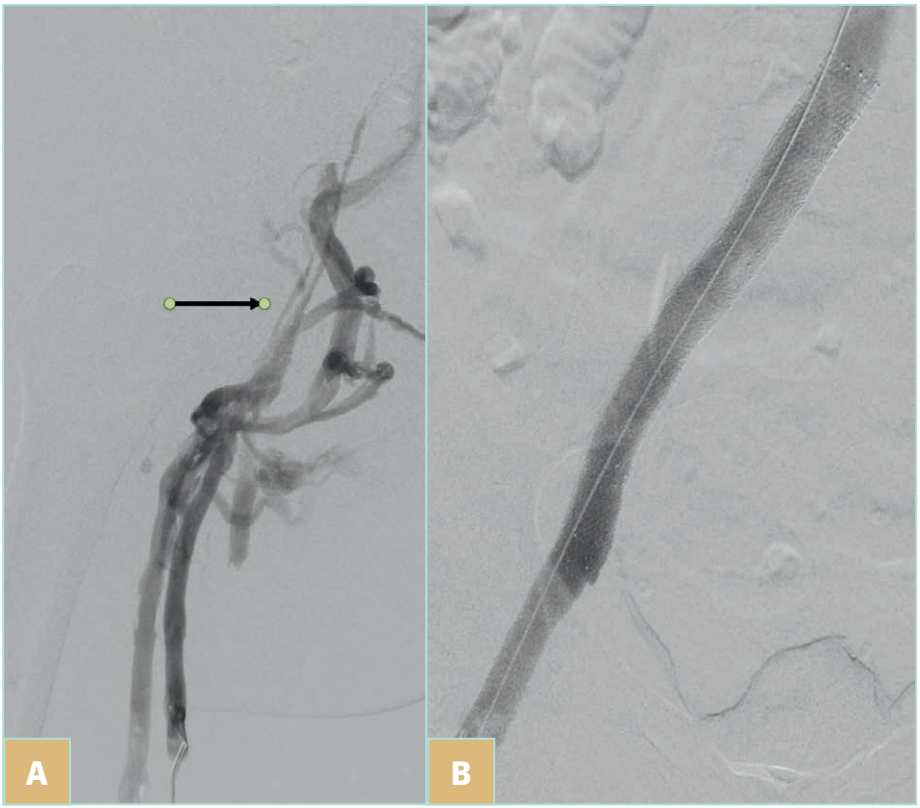

Figure 1. Postthrombotic left iliofemoral venous obstruction. A) Digital subtraction left common femoral venography of a patient in the prone position demonstrates postthrombotic obstruction of the left common femoral and left iliac vein. The arrow denotes the true lumen of the occluded iliac vein; other veins represent collateral drainage. B) Venography after stent placement demonstrates recanalized left common femoral and left iliac vein; collaterals are no longer visualized.

Thoracic central venous obstruction

While obtaining a history and physical examination, specifically evaluate for the cause and risk factors for the occlusion, as well as the time course and severity of symptoms, which will dictate urgency of intervention.

As TCVO can be caused by numerous factors and can have varying extents of disease, it is important to evaluate imaging to determine the feasibility and durability of a potential intervention. For example, in patients with SVC syndrome, it is important to assess the extent of SVC occlusion and cause (tumor, catheter/device). Focal SVC lesions tend to have better outcomes as inflow is preserved; involvement of inflow veins (eg, innominates/subclavian) can have a significant negative impact on long-term patency and treatment options. In vTOS, imaging can identify the compression lesion as well as the presence of associated acute thrombus, which would require concomitant thrombectomy/thrombolysis. In catheter/device-related occlusions, imaging assists in evaluating the ongoing need for devices (eg, dialysis catheters, cardiac leads), as well as potentially involves the necessary subspecialists to assist in decision-making regarding necessity of intervention and/or device placement following recanalization.

Procedure

There are significant similarities in basic procedural techniques in deep venous recanalization, which are summarized in a stepwise fashion below. Where there are differences or variations, they are specifically noted.

Postthrombotic lower-extremity deep venous obstruction

1. Select a primary venous access site. The primary consideration is to ensure that inflow into a stent is preserved.
    a. If the CFV is uninvolved, either CFV or great saphenous vein adjacent to the saphenofemoral junction may be used.
    b. If the CFV is involved, either popliteal, small saphenous, posterior tibial, mid-thigh femoral, or internal jugular vein access may be used per operator preference. CFV access would compromise inflow and would place the stent at risk for occlusion.
    c. For iliocaval or other complex occlusions, multiple accesses are necessary to visualize normal/pathologic anatomy and facilitate traversal of the occlusion.
2. Using a linear high-frequency ultrasound transducer for guidance, administer local anesthetic to the soft tissues and obtain ultrasound-guided access.
3. Place a sheath at the access site; typical sizes needed for chronic occlusions are 9 Fr or 10 Fr.
4. Perform venography to assess the extent of the occlusion.
5. Traverse the occlusion with a wire and catheter; most commonly, hydrophilic wires are used. Attempt to identify the occluded vein, which may be obscured by collaterals, by performing multiplanar venography *(Figure 1)*. Note, a crossing/support catheter may be necessary to provide sufficient support for crossing the occlusion. The use of sharp/radiofrequency techniques is common but carries increased procedural risk and should only be performed by experienced operators.
6. Perform venographic confirmation of traversal into normal venous anatomy; pay specific attention to ensure that collateral vessels/azygos system are not mistaken for the IVC.
7. Perform intravascular ultrasound (IVUS) to assess the length of the occlusion (using both markers on the catheters and imaging findings), the inflow vessels (ie, PFV) in the event of CFV compromise, and cranial/caudal stent landing zones. Note, IVUS is of limited utility in selecting stent diameter in PTS given that there frequently is not a suitable "normal" reference vessel to measure.
8. Administer systemic anticoagulation prior to predilation and stent placement; typically 70-100 units/kg unfractionated heparin or bivalirudin/argatroban in patients with heparin-induced thrombocytopenia. It may be helpful to monitor activated clotting time through the remainder of the procedure at approximately 30-minute intervals, with a target of 200-300 seconds.
9. Pre-dilate the occluded venous segments to the target stent diameter via balloon angioplasty; typically, 14-16 mm in iliac veins and 12-14 mm in the CFV. The diameter chosen will depend upon the stent model that is selected. In the event of an iliocaval occlusion, pre-dilate to the target diameter of the selected stent; note that as of present, there are no on-label IVC stents, and there are several approaches to IVC stent placement, including stents designed for tracheobronchial applications, larger diameter iliofemoral approved stents, and placement of iliofemoral stents in a "double-barrel" configuration. Consider balloon angioplasty of the inflow vessels as needed to optimize inflow.
    a. If an IVC filter was the cause for iliocaval occlusion, consider retrieval based on local filter retrieval expertise.[11]

10. Deploy on-label self-expanding venous stents in the occluded segments. Stent placement below the inflow of the PFV (roughly at the level of the lesser trochanter) is rarely performed due to low patency rates.

    a. Sizing of stents depends on whether nitinol stents (which deploy true to size) or Elgiloy stents (a woven stent which has variable diameter based on its deployed length) are chosen.

11. Perform post-dilation balloon angioplasty of each stent to its rated diameter.

12. Perform venography and IVUS to assess luminal restoration and determine if there is adequate flow. Ensure that there is adequate coverage of the lesion by the stents.

13. Remove the sheath and achieve hemostasis with direct compression.

Variations in the procedure for NIVL

1. Nonthrombotic lesions can typically always be treated from groin (CFV, great saphenous) access.

2. IVUS has a significantly different role in NIVLs, as in most cases there is a ''normal'' reference segment. Classic teaching has been to select patients with at least 50% area stenosis at the lesion site relative to a normal vein segment; newer data suggests that patients that improve with stent placement typically have a >61% minimum diameter stenosis relative to a normal vein segment *(Figure 2)*.[12] Ensure that you do not compare with a prestenotically dilated common iliac vein; typically, the best segment for comparison is the external iliac vein. Similarly, use the external iliac vein as the reference segment when selecting stent size for placement; follow the instructions for use for sizing (there is some oversizing that is typical). Analysis of the published literature suggests that stents shorter than 60 mm in length and smaller than 14 mm in diameter had a greater likelihood of migration.[13]

3. Baseline therapeutic anticoagulation may not be necessary; these patients do not have thrombotic disease. Intraprocedural anticoagulation may be sufficient.

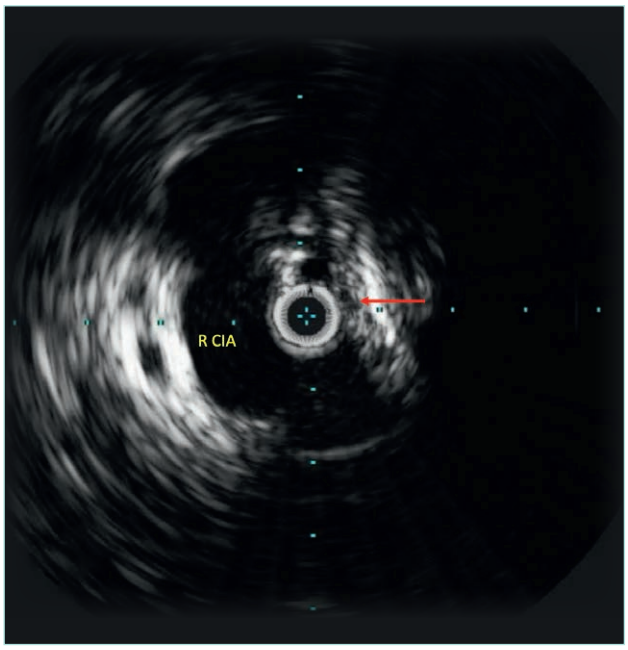

Figure 2. 10-MHz Intravascular ultrasound of the left common iliac vein (red arrow) demonstrates compression by the right common iliac artery (R CIA). Note that the vein wall is thickened and echogenic.

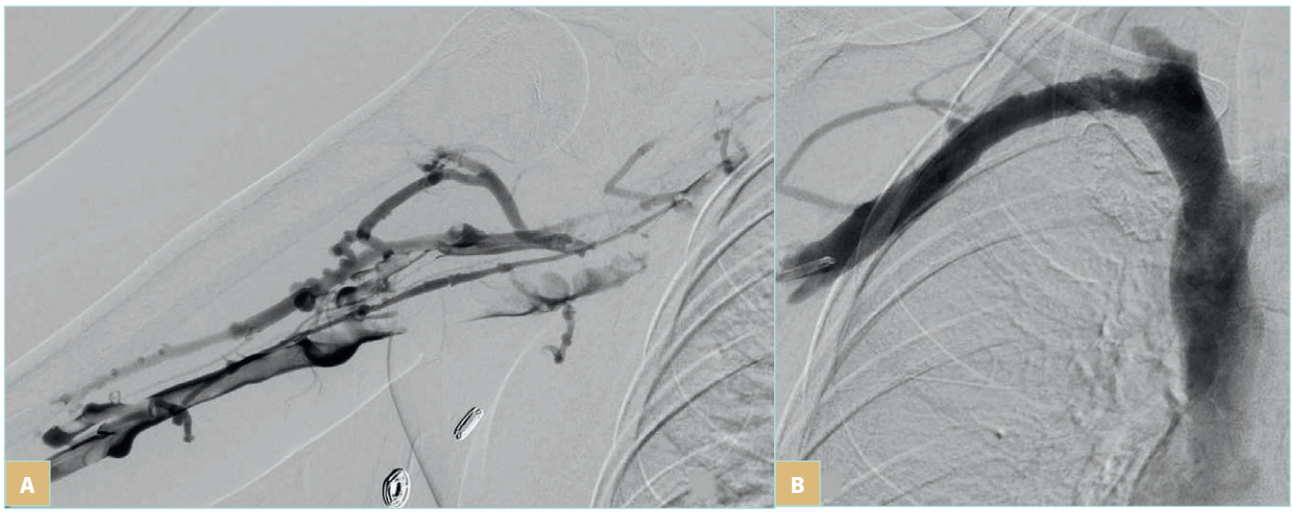

Figure 3. Acute right subclavian vein thrombosis. A) Digital subtraction right basilic venography demonstrates acute thrombotic occlusion through the axillosubclavian veins on the basis of venous thoracic outlet compression. B) Right subclavian venography following thrombectomy and angioplasty of the compression demonstrates subtotal luminal restoration. This patient went on to have transaxillary first rib resection to remove the cause of extrinsic compression.

Variations in the procedure for TCVO

1. Typical access sites are basilic, brachial, or cephalic veins. If additional sites are needed for complex occlusions, groin venous access may be of value.

2. Many of the tools for traversal of chronic lower-extremity postthrombotic occlusions apply here as well. Again, the use of sharp/radiofrequency techniques is common but carries increased procedural risk and should only be performed by experienced operators. Risks include mediastinal, lung, or cardiac injury, including tamponade. If using such techniques in close proximity to the heart, adequate surgical backup and preparation for emergent chest or pericardial drainage is mandatory.

3. For vTOS/Paget-Schroetter syndrome with acute thrombus, perform thrombectomy with a device of the operator's choice *(Figure 3)*. Notably, stent placement in these patients is not advised due to the high risk for stent fracture at the mechanical compression site, typically between the clavicle and first rib. Stent placement in this location should be reserved for highly selected scenarios with limited options.

4. No stent is specifically approved for used in TCVO, thus all placements are off-label. Stent size selection is variable with minimal data to provide guidance. Typically, 12- to 14-mm stents in the innominate veins are sufficient. For focal SVC stenosis, consider using IVUS to measure the uninvolved portion of the SVC for guidance on stent selection.

5. For extensive reconstructions involving subclavian and innominate veins and SVC, ensure that the patient's symptoms are severe enough to dictate that an intervention is likely to be helpful, and that the inflow into the occluded segments appears sufficient to support stent patency.

Results

Postthrombotic recanalization results: A meta-analysis demonstrated a 1-year primary patency of 79% and 5-year projected patency of 60%.[14] However, this data was with many stents being placed off-label and before techniques for treatment of PTS were refined to the level used today. Furthermore, several new on-label venous stents are available, which will lead to the generation of new data.

NIVL treatment results: Meta-analysis data suggests high primary patency rates at 1 year, approximately 96%, and projected 5-year patency rates of approximately 90%.[14] These high patency rates are corroborated in numerous investigational device exemption trials.

TCVO recanalization results: Outcomes are difficult to assess, given the variety of anatomy that may be involved, the different contributing comorbidities, the lack of systematic approaches to treatment, and the lack of follow-up. Limited data are available on the treatment of Paget-Schroetter syndrome, with a meta-analysis suggesting clinical improvement in approximately 90% following thrombectomy and surgical decompression.[15]

Postprocedure management

For patients with postthrombotic occlusions or extensive TCVO, including vTOS/Paget-Schroetter syndrome, anticoagulation should be administered post procedure. LMWH is preferable early in the postprocedural course per expert consensus, due to its pleiotropic anticoagulant and anti-inflammatory effects. At 4 to 6 weeks, it likely can be transitioned to an oral agent. The duration of anticoagulation will depend on the nature and severity of disease, as well as the patient's prior thrombosis history. Consider comanagement with a hematologist.

The use of antiplatelet agents in the setting of stents is controversial with little supporting data. Consider a short period of clopidogrel (3 months) followed by low-dose aspirin (81 mg) indefinitely. As stated above, NIVL patients may not require anticoagulation or antiplatelet therapy.

Compression therapy for lower-extremity disease should be encouraged for symptom reduction. Starting at lower intensity, such as 20- to 30-mm-Hg compression, is reasonable if compliance is a concern; for severe postthrombotic disease, consider 30 to 40 mm Hg or higher, as tolerated. For patients with a component of phlebolymphedema, consider lymphedema therapy, including manual lymphatic drainage and pneumatic compression.

Imaging follow-up will be dictated by local preference and expertise and can include duplex ultrasound or CTV. MRV will be of limited utility for assessing stent patency due to metal-related susceptibility artifact. Perform imaging and clinical follow-up at 1 month. Ongoing long-term follow-up should be considered for patients with extensive postthrombotic disease or complex TCVO, as reintervention may be needed to assist patency and address symptom recurrence.

Complications

Common procedural complications can occur, including bleeding from the access or intervention site, or infection related to an invasive procedure, including site infection or stent infection. Serious complications of this nature are rare with proper technique.

Pulmonary embolism is a very rare complication in this type of procedure.

Stent occlusion is a complication that is not fully understood. The short-term consequences of loss patency and recurrence is known; however, the effect of a permanently implanted malfunctioning device is not.

Patients with chronic venous disease often require long-term anticoagulation, which carries a risk of bleeding diatheses. Ongoing assessment of the need for anticoagulation should occur in patients on long-term therapy.

Conclusion

The endovascular management of chronic venous obstructive disease has witnessed significant growth, mirrored by the rapid pace of device innovation and ongoing robust clinical trials. As more data emerges, proper patient selection, technical expertise, and diligent follow-up are necessary to ensure optimal outcomes.

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Current status of venous stenting and a look at where we need to go

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ABSTRACT

Venous stenting has rapidly advanced over the last 10 years as the emergence of dedicated venous stents and advancement in thrombectomy devices has renewed interest in this field. This rapid advancement has seen the introduction of several new devices, which have now gained market approval. Inevitably, the advancement of technology has outpaced the evidence to support the use of such devices, and complications have arisen as the number of patients treated has rapidly expanded. The lack of evidence has been compounded by difficulty in completing and recruiting for randomized trials, which has meant guidelines have needed to rely on cohorts and expert consensus for recommendations. Despite the inevitable growth difficulties, the options now available for patients are significantly wider, and future advancements in technology will likely improve options and long-term results. This is needed for a group of patients who continue to suffer with the debilitating effects of chronic venous disease.

Keywords

big data | data | randomized controlled trials | rapid technological advancement | registries | venous stenting

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Introduction

Venous stenting for the treatment of chronic venous disease rose to prominence following a seminal publication by Neglen and Raju.[1] These papers highlighted the potential for stenting to address the chronic venous hypertension caused by iliac outflow obstruction. In addition, it became clear as thrombectomy practice evolved that stenting of underlying lesions played an important role in the success of these treatments in preventing postthrombotic syndrome (PTS).[2]

This paper reviews the advancements we have seen in the last several years, addresses some of the problems that have arisen, and assesses potential future developments that may be needed.

Dedicated venous stents

The biggest development in the last 10 years has been the emergence of dedicated venous stents. The focus has been on stents designed specifically for the unique venous environment rather than using arterial stents off-label. The dedicated stents have also benefited from newer platforms that have improved ease and accuracy of deployment.[3]

This evolution has seen 4 stents receive market approval in the United States following Investigational Device Exemption (IDE) studies, and several new devices have emerged in the European and Outside United States (OUS) markets.[4-7] The results of these studies are collated in *Table I* and show outcomes out to 3 years. In addition to the IDE studies, other studies have published outcomes with now several different stents on the market.[8,9]

All of the studies have shown broadly similar outcomes with no data to suggest that any one stent performs significantly better than another.[10] However, the studies have confirmed that PTS patients with occlusion have worse outcomes than those with a stent placed following thrombolysis for acute thrombotic (AT) events. As expected, nonthrombotic iliac vein lesions (NIVLs) have significantly better long-term patency. Direct comparison is not straightforward though as classification and outcome measures were not universally the same. Despite these limitations, the conclusion remains that dedicated venous stents have resulted in a substantial increase in attention to the treatment of these patients. However, long-term results have not yet realized the patency gains promised by the initial technological advances.

Regardless of patency, several studies have shown that treatment of patients with PTS, NIVL, and AT lesions does significantly improve long-term quality of life (QOL) outcomes, with these improvements sustained over time.[11-13] In addition, a study from Italy has suggested that venous stenting is likely to be cost-effective, especially when considering moderate and severe disease.[14] This is particularly important when we consider the cost associated with the burden of leg-ulcer care in which venous stenting may play a significant role.[15,16]

Trial Device	ABRE Abre (Medtronic)				VERNACULAR Venovo (BD)				VIRTUS VICI (Boston Scientific)				VIVO Zilva Vena (Cook Medical)			
Baseline	Overall	Acute	Chronic	NIVL	Overall	Acute	Chronic /Acute	NIVL	Overall	Acute	Chronic	NIVL	Overall	Acute	Chronic	NIVL
Numbers	200	72	95	33	170	NA	93	73	170	NA	127	43	243	59	105	79
MAE at 30 days	2%				6.5%				1.2%				3.3%			
Primary patency	Overall	Acute	Chronic	NIVL	Overall	Acute	Chronic	NIVL	Overall	Acute	Chronic	NIVL	Overall	Acute	Chronic	NIVL
12	88%	87.1%	79.8%	98.6%	88.6%	NA	81.7%	97.1%	84.6%	NA	79.8%	96.2%	89.9%	89.1%	83.1%	100%
24	86.2%	83.3%	76.8%	98.6%	84.4%	NA	75.6%	95.4%	79.7%	NA	73.8%	97.1%	90.3%	84%	86.1%	100%
36	81.6%	76.5%	70.4%	97.1%	79.5%	NA	70%	93.6%	71.7%	NA	64.1%	96.4%	90.3%	84%	86.1%	100%

MAE, major adverse events; NIVL, nonthrombotic iliac vein lesion.

Table I. Primary outcomes (major adverse events at 30 days and primary patency) of the 4 completed Investigational Device Exemption (IDE) studies.

Guidelines and randomized trial data

Based on the available data, venous stenting was given a grade IIa recommendation in the European Society of Vascular Surgery guidelines for both acute and chronic disease.[17,18] However, the recommendation was based primarily on expert opinion and limited studies, highlighting the paucity of robust evidence to support stenting.

Only 2 randomized controlled trials (RCTs) have been published. The first was a small series from Brazil that suggested a significant benefit.[19] The second was the planned, larger STEVECO trial (Stent Versus Conservative Treatment in Patients With Deep Venous Obstruction), although it failed to meet its recruitment target. The difficulties faced in the later study highlight the difficulty in completing venous RCTs. This was clear in treatment of AT where both ATTRACT (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) and CAVA (CAtheter Versus Anticoagulation alone for acute primary [ilio]femoral DVT) trials took 10 years to complete recruitment.[20,21] Larger RCT's in PTS—C-TRACT (NCT030250247; Chronic venous Thrombosis: Relief with Adjunctive Catheter-directed Therapy) and BEST-PTS (NCT05622500; Best Endovenous Treatment, Including STenting, Versus Non-endovenous Treatment in Chronic Proximal Deep Venous Disease)—are experiencing similar issues with recruitment delays, and IGuideU (NCT04696354; Intravascular Ultrasound-Guided Intervention for Venous Leg Ulcers) was terminated early after recruitment problems meant the study could not meet its timeline.

These recruitment difficulties are the consequence of both patients and clinicians struggling with equipoise. In the case of the former, patients often demand treatment for conditions for which they have frequently struggled with inadequate medical management. When they are referred to centers that offer intervention, they refuse randomization. In the case of clinicians who are engaged in treatment, the decision to offer randomization is met with resistance.

Without this evidence, there will continue to be struggles to show clearly that these treatments should be offered. Importantly, this will not overcome resistance to refer patients for consideration for treatment from clinicians who are guided by current trial data. Trial evidence is a necessity to influence payors and organizations such as the National Institute for Clinical Excellence (NICE) in the United Kingdom who provide treatment guidance.

Therefore, there is a significant need to consider multiple alternative strategies to collect data that supports these treatments. This may be provided by registries established independent of the IDE studies, perhaps supported by societies. Well-established registries can provide the necessary multicenter prospective cohort data; however, a weakness lies in the absence of control groups. This weakness may be overcome, and it is necessary to do so to ensure there is an appropriate comparator arm. Nonetheless, even if this weakness is overcome, registries suffer from inherent bias that means the data produced is not viewed on a level with RCTs.

The stronger, and perhaps likely answer lies in so-called ''big data.'' In the case of large-scale data collection, opportunities arise in formal data analysis techniques such as causal inference, which allow a similarly robust bias mitigation afforded by RCTs.[22] The advantage of these study designs is that patients do not need to be randomized and can be treated as the primary clinicians and patients choose.

Whatever choice is made, venous stenting requires more robust data, and it is incumbent upon clinicians who wish to see these treatments advance to commit to studies. This absence of data was critically highlighted when stent migration forced the withdrawal of the VICI stent (Boston Scientific).

Migration problem

The VICI stent withdrawal demonstrated the risk inherent in rapid technological advancement.[23,24] Migration, though a known risk, had not been seen in the IDE studies and during the early phase of stent development had not been widely reported. However, a review of the literature suggests the problem may be underreported and concluded that it was principally associated with using short and undersized stents.[25] Furthermore, it was highlighted that inappropriate patient selection was a factor.

The focus on appropriateness that has followed the migration debacle demonstrates that significant gaps in training and education need to be addressed. Clinicians and Industry need to work in parallel to build programs that support technical skill acquisition, as well as patient pathway and decision-making paradigms. The publication of an article in the *New York Times* that focused on peripheral arterial disease makes clear the dangers that lie ahead for this field if such issues are not addressed.[26] Appropriateness involves ensuring treatment is only offered to patients who need it.

Future developments

The lack of data has been addressed above but will remain a central issue regardless of parallel technological advancements. A fundamental problem, in addition to those addressed previously, has been the choice of study outcome measure.[27] ATTRACT has faced significant criticism for its use of the Villalta score, particularly in adopting a binary approach, whereas STEVECO likely failed by choosing a 14-point improvement in the VEINES-QoL questionnaire score (VEnous INsufficiency Epidemiological and economic Study – Quality of Life) as the primary outcome measure for the study. Both trials had significantly positive outcomes in favor of patient treatment, yet the primary measure did not show this. The future of studies rests on better defining outcome measures for venous disease.

Some efforts have been made through the International Consortium on Health Outcome Measures (ICHOM) process.[28] That process highlighted several outcome measures that should be considered and, as a strength, incorporated patient-centered outcome measures. This review could only focus on existing tools, and it is clear from the lengthy list of necessary outcome measures that a better understanding of those features that really drive outcomes is needed. We are likely to see advances in this understanding and have seen some advances with the development by Houman Jaiaie of a system for classification of venous patients, which may help to standardize reporting and allow for more direct comparison between studies; however, at the moment, this classification has not yet been validated.

Technological advances in stent design are also inevitable and, as in other disease states, likely to outpace data collection. Current stents are largely all laser-cut nitinol designs with some variation between open and hybrid designs incorporating closed-cell elements. Future stent designs are likely to build on this by incorporating drug coating and alternative designs that attempt to influence factors like the Poisson effect or flow. The direction of travel is currently limited by a clear understanding of what factors drive patency loss and the biological mechanism of stent thrombosis and occlusion. It is imperative that a better understanding of the mechanism of stent failure is developed.

The IDE studies have all shown that the 3-year occlusion rate in PTS patients is approaching 30%. This underscores that improvements are needed but also indicates that there is a group of patients with blocked stents who will need treatment. We will see advances in creating tools suited to these patients with technology to remove the fibrotic tissue that builds up with stents. The current approach of simply ballooning stents is inadequate.

These advances are likely to focus on drug delivery; trials are already underway to assess the impact of dexamethasone administration into the vessel wall. Two DEXTERITY studies (NCT04858776 [Perivenous Dexamethasone Therapy: Examining Reduction of Inflammation After Thrombus Removal to Yield Benefit in Subacute and Chronic Iliofemoral DVT (DEXTERITY-SCI)] and NCT04862468 [Perivenous Dexamethasone Therapy: Examining Reduction of Inflammation After Thrombus Removal to Yield Benefit in Acute Femoropopliteal DVT]) raise the possibility that so-called "vessel preparation" may be a factor in improving outcomes in PTS patients, possibly negating the need for stenting in AT patients. Drug delivery to the wall in addition to coating on stents is an intriguing prospect, but it is not clear yet if a coating is to be added and what that coating should be.

Conclusion

Venous stenting has evolved rapidly in the last decade with several new devices reaching the market. This has seen treatment volumes increase but perhaps in advance of the data supporting these interventions. The next several years should see development of better reporting methods, as well as advancement in technology. The technological advancements are likely to focus more on adjunctive technologies that support the whole procedure rather than simply the stent itself.

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